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Smoking Cessation and the Risk of Hyperactive Delirium in Hospitalized Patients: A Retrospective Study

Cessation du tabagisme et risque de délire hyperactif chez les patients hospitalisés: une étude rétrospective

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Abstract

Objectives: The acute cessation of smoking often induces symptoms that are similar to those associated with delirium. We aimed to evaluate effects of sudden nicotine abstinence on the development of delirium and its motoric subtypes in hospitalized patients.

Methods: The present study included patients who were referred to psychiatrists by ward physicians due to confusion. The presence of delirium was defined using the Confusion Assessment Method and the Delirium Rating Scale Revised–98, which was also used to assess the severity of delirium. Outcome variables, including the length of hospital stay and 3-month mortality rate, were collected by a retrospective chart review.

Results: Delirium was confirmed in 210 of the 293 referred patients. Of the motoric subtypes of delirium, the hyperactive subtype was more common (68.1%) and was related to higher 3-month mortality (odds ratio [OR], 2.189; 95% confidence interval [CI], 1.07 to 4.49; $P = 0.033$) compared with hypoactive delirium. Patients undergoing sudden cessation of smoking ($n = 55$) were more likely to exhibit hyperactive delirium than were nonsmokers ($P = 0.001$). A multivariate analysis revealed that smoking cessation was an independent risk factor for hyperactive delirium (OR, 10.33; 95% CI, 2.31 to 46.09; $P = 0.002$). In addition, the amount of smoking was positively correlated with the severity of hyperactivity ($r = 0.421$, $P = 0.003$). Smoking status did not significantly influence overall delirium incidence.

Conclusions: The present findings demonstrated that nicotine withdrawal was associated with hyperactive delirium, which suggests that they share common pathophysiologies that involve the dopamine, opioid, and cholinergic systems.

Abrégé

Objectifs : La cessation aiguë du tabagisme comporte souvent des symptômes qui sont semblables à ceux associés au délire. Nous visions à évaluer les effets de l'abstinence soudaine de nicotine sur le développement du délire et de ses sous-types moteurs chez les patients hospitalisés.

Méthodes : La présente étude incluait des patients qui ont été référés à des psychiatres par des médecins de service en raison de leur confusion. La présence du délire a été définie à l'aide de la méthode d'évaluation de la confusion et de l'échelle révisée-98 d'évaluation du délire, qui a également servi à évaluer la gravité du délire. Les variables des résultats, y compris la durée du séjour à l'hôpital et le taux de mortalité de 3 mois, ont été obtenues par une revue rétrospective des dossiers.

Résultats : Le délire a été confirmé chez 210 des 293 patients référés. Parmi les sous-types moteurs du délire, le sous-type hyperactif était plus commun (68,1%) et était lié à une mortalité de 3 mois plus élevée (RC 2,189; IC à 95% 1,07 à 4,49;

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p = 0,033) comparé avec le délire hypoactif. Les patients subissant une cessation soudaine du tabagisme (n = 55) étaient plus susceptibles de présenter un délire hyperactif que les non-fumeurs (p = 0,001). Une analyse multivariée a révélé que la cessation du tabagisme était un fateur de risque indépendant du délire hyperactif (RC 10,33; IC à 95% 2,31 à 46,09; p = 0,002). En outre, la quantité du tabagisme était positivement corrélée à la gravité de l'hyperactivité (r = 0,421; p = 0,003). L'état du tabagisme n'influençait pas significativement l'incidence globale du délire.

Conclusions : Les présents résultats ont démontré que le sevrage de la nicotine était associé au délire hyperactif, ce qui suggère qu'ils partagent des pathophysiologies communes qui impliquent les systèmes dopaminergique, opioïde et cholinergique.

Keywords
smoking, nicotine withdrawal, hyperactive delirium, mortality

Clinical Implications

- Acute nicotine withdrawal was associated with the development of hyperactive delirium and severe agitation in hospitalized patients.
- Hyperactive delirium was related to increased mortality, and thus smoking cessation should be cautiously managed in patients at risk of delirium.
- Future research should evaluate the potential usefulness of nicotine replacement treatment for the prevention of hyperactive delirium in hospitalized smokers.

Limitations

- Our study examined the history of smoking rather than nicotine withdrawal–related symptoms.
- We investigated patients referred to a consultation-liaison psychiatry; it is unclear that these results can be generalized to other populations.

Delirium is a neurocognitive disorder that develops commonly in hospitalized patients.[1] This disorder is currently defined by the abrupt onset of disturbances in consciousness, attention, and cognition that tend to have fluctuating courses.[2] Delirium is associated with a variety of poor outcomes, including increased morbidity and mortality and longer hospital stays.[3,4] Lipowski[5] described 3 subtypes of delirium based on arousal and psychomotor behaviour: hyperactive (hyperalert or agitated), hypoactive (hypoalert or lethargic), and mixed. Webster and Holroyd[6] suggested that hyperactive delirium is most often characterized by agitation, disorientation, and hallucinations, whereas hypoactive delirium is characterized by sedation and confusion. In addition, each delirium subtype has a different pathophysiology, and hence each responds differently to treatment.[7,8] Taken together, these findings support the clinical utility of subtyping delirium.

During hospital stays, patients who are smokers are often asked to temporarily quit smoking, and they can sometimes experience acute nicotine withdrawal. Nicotine withdrawal and delirium, particularly hyperactive delirium, share common pathophysiology and have similar clinical features, including confusion, agitation, and irritability.[9] The time courses of nicotine withdrawal and delirium are also similar, with both peaking within the first several days after the beginning of nicotine abstinence or onset of delirium, respectively, following hospitalization.[10] Acetylcholine deficiencies have been shown to play a crucial role in the pathophysiology of nicotine withdrawal; more specifically, upregulation and desensitization of nicotinic acetylcholine receptors have been identified in the brains of chronic smokers, and in the unoccupied state of abrupt abstinence, they contribute to the manifestation of withdrawal symptoms.[11] Accordingly, one convincing hypothesis proposes that delirium results from cholinergic deficits.[12] Several other neurotransmitter systems, including the dopamine, serotonin, gamma-aminobutyric acid, and opiate systems, are also involved in the manifestation of nicotine withdrawal symptoms.[13] The abrupt occurrence of imbalances within these neurotransmitter systems has also been implicated in the pathophysiology of delirium.[14]

Given the impact of delirium on behavioural functioning and health care costs, the importance of identifying the risk factors for this condition and preventing its occurrence has been increasingly emphasized.[15] Several studies have evaluated whether smoking is a risk factor for delirium. Nearly all of these studies were carried out using critically ill intensive care unit (ICU) populations, and they produced conflicting results.[16] Furthermore, the relationship between nicotine withdrawal and the hyperactive subtype of delirium has yet to be evaluated. Thus, the present study aimed to explore the effects of sudden nicotine abstinence on the development of delirium and its motoric subtypes in hospitalized patients. A dose-response relationship was identified between the cumulative dose of smoking and the severity of delirium and agitation.

Methods

Patients and Assessment

The present study included patients who were referred by ward physicians to consultation liaison (CL) psychiatry at Seoul National University Bundang Hospital in Seongnam City, Republic of Korea, due to confusion. During the evaluation and management of these patients, psychiatrists assessed their clinical features and collected demographic data such as age, sex, and the level of education. All referred patients were assessed for the delirium using both tools, the

Delirium Rating Scale Revised–98 version (DRS-R98)[17] and the Confusion Assessment Methods (CAM).[18] Patients who fulfilled the diagnostic criteria of 1 of 2 tools were diagnosed with delirium following an assessment by trainee psychiatric residents under the supervision of a professional psychiatrist.

The CAM was developed to screen for delirium based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*.[19] It evaluates 4 key features: 1) acute onset or fluctuating course of change in mental status, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness, which is rated using the Richmond Agitation–Sedation Scale (RASS) on a scale ranging from −5 (unarousable) to +4 (combative).[20] A diagnostic algorithm based on CAM provides a diagnosis of delirium according to the presence of both acute onset or fluctuating course and inattention as well as either disorganized thinking or altered level of consciousness.

The DRS-R98 was designed for the phenomenological assessment of delirium via the use of Likert scale ratings of 16 descriptive items encompassing 13 severity items and 3 diagnostic items. Each item is rated on a scale ranging from 0 (absent) to 3 (severely impaired), and the cut-off score for delirium is 18 points on the total score. This measure has high interrater reliability, validity, sensitivity, and specificity for distinguishing delirium from other neuropsychiatric disorders such as dementia and depression.[17] Aetiologies related to delirium, including a physical diagnosis, psychiatric comorbidity, history of smoking or alcohol consumption, and current medication, are also assessed and recorded in the psychiatric notes on the patient's electronic medical chart. All patients were routinely asked to provide details about their smoking habits to ward nurses as part of the standard admission assessment at Seoul National University Bundang Hospital. In addition, psychiatrists obtained the following details about the lifetime smoking history during a clinical assessment in the consultation: current, former, or never smoker; average number of packs smoked daily; number of years smoked; and time of cessation. These admission notes and psychiatric notes were reviewed to explore associations between smoking and delirium. Smoking exposure was calculated in pack-years as follows: average number of packs smoked per day multiplied by number of years smoked.

The protocol of the present study was approved by the Institutional Review Board of Seoul National University Bundang Hospital with the waiver of informed consent to review electronic medical charts.

Study Procedure

In the present study, the psychiatric and medical records of patients who were referred to the CL psychiatry due to confusion between March 2013 and December 2013 were reviewed. The data of the patients who were diagnosed with delirium were obtained from a retrospective chart review, and information on age, sex, clinical profile, and ratings on the CAM and DRS-R98, as well as later outcomes such as the length of hospital stay and 3-month mortality, were obtained. Patients who had experienced a coma, had a focal neurological deficit, had a history of alcohol use disorder, or experienced confusion starting before admission were excluded. A single researcher (H.Y.P.) reviewed the medical charts of all patients to minimize interrater variability.

The patients were divided into 2 groups: the smoker group, which included patients who had undergone acute abstinence from smoking after admission, and the nonsmoker group, which included patients with no history of smoking or with tobacco discontinuation >1 month prior to admission. Symptoms of tobacco abstinence are known to last 2 to 4 weeks, and thus 1 month of smoking discontinuation was required for inclusion in the nonsmoker group to minimize the effects of nicotine withdrawal.[21] To measure the overall severity of delirium, the total score on the 16 DRS-R98 items was calculated for each patient; total severity scores on the DRS-R98 range from 0 to 48, with higher scores indicating more severe delirium. Next, the patients with delirium were classified into hypoactive and hyperactive delirium subtypes as in previous studies.[22,23] Hyperactive delirium was defined as a positive score and hypoactive delirium was defined as a negative score on the RASS.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 18 (SPSS, Inc., an IBM Company, Chicago, IL, USA). Pearson χ^2 tests or Fisher exact tests were used to analyze the baseline demographic and clinical variables as well as all categorical variables, and Student's *t* test was used to analyze all continuous variables. To assess the risk of the smoking cessation for both delirium and motoric subtypes, binary logistic regression with the backward selection was used and all baseline variables were included as covariates: age, sex, education, comorbidities, and medical diagnosis. Sex, comorbidities, and smoking cessation were dichotomous variables (female, absence of dementia, hypnotics use and opiates use, and no smoking cessation as the reference category). Age was included as a continuous variable, and educational level and medical diagnosis were categorized variables.

In addition, a 2-tailed Spearman's correlation analysis was conducted to evaluate the relationships among the variables. All tests were 2-tailed, and a P value <0.05 was considered to indicate statistical significance. In the present sample of hospitalized patients, there was a 17.3% baseline incidence of smokers, and this number was used to calculate the sample size necessary to achieve a 35% absolute difference in delirium incidence among smokers and nonsmokers; the required sample size for a power of 0.80 and $\alpha = 0.05$ was 123 participants.

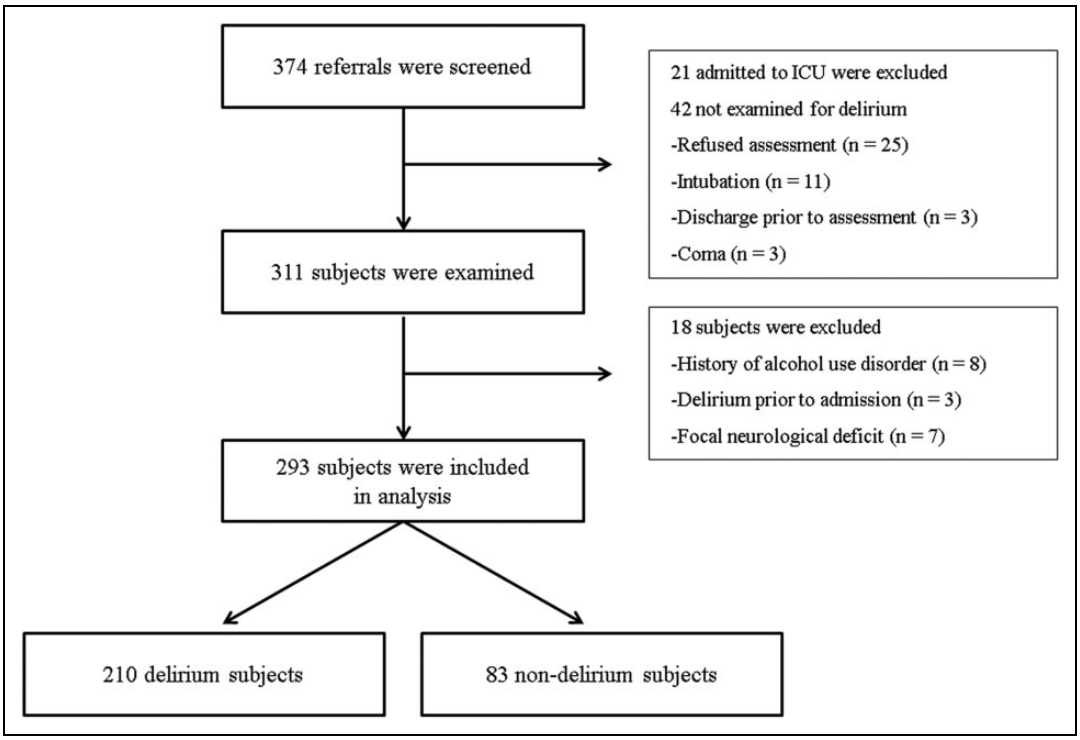

Figure 1. Study enrollment. ICU, intensive care unit.

Results

Patients and Delirium

During the study period, 374 referrals were screened for their initial assessment of delirium, as shown in Figure 1. The mean ± SD time interval between the first observed symptom of confusion and the initial psychiatric referral was 5.18 ± 9.27 days. Of the 374 consecutive referrals, 311 patients met the inclusion criteria for the present study, and 63 ineligible patients were excluded: admission to ICU (21), refused assessment (25), intubation (11), discharge prior to assessment (3), and coma (3). Eighteen patients were secondarily excluded, resulting in a total of 293 patients for the final analyses of the present study. Of the 293 patients remaining, 210 (71.7%) were diagnosed with delirium, and nondelirious status was determined in 83. Among the various clinical and demographic variables assessed in the present study, only medical diagnosis was significantly related to the incidence of delirium after controlling covariates (odds ratio [OR], 2.45; 95% confidence interval [CI], 1.28 to 7.45; $P = 0.007$). Specifically, a diagnosis of septic shock, cardiac disease, neurological disease, or infection was more prevalent in patients with delirium than in those with confusion without confirmed delirium. In addition, the delirious patients had a significantly higher mean ± SD severity score for the total DRS-R98 scores than did nondelirium patients with confusion (21.51 ± 5.22 vs. 12.45 ± 3.80; $P < 0.001$).

Motoric Subtypes of Delirium

Of the 210 patients with delirium, 143 (68.1%) were diagnosed with the hyperactive subtype, and 67 were diagnosed with the hypoactive subtype (Table 1). In the present study, patients with hyperactive delirium showed higher severity scores and higher degrees of sleep disturbances and mood lability, but the length of hospital stay and 3-month mortality did not significantly differ between patients with hyperactive and those with hypoactive delirium. However, a multivariate logistic regression analysis revealed that the hyperactive group had higher 3-month mortality than the hypoactive group after controlling for covariates of age, sex, comorbidities, and medical diagnosis (OR, 2.19; 95% CI, 1.07 to 4.49; $P = 0.033$).

Associations between Smoking and Delirium Subtype

The demographic information, clinical characteristics, and outcomes of the patients are presented in Table 2. The smoker group had a younger mean age and a greater proportion of males, and although the incidence of delirium was not related to smoking status, the smoker group had a higher proportion of patients who exhibited the hyperactive subtype than did the nonsmoker group (94.9% vs. 62.0%, respectively; $\chi^2 = 15.81, P < 0.001$). The mean scores on the RASS and on DRS-R98 items 1, 4, and 7 significantly differed between the smoker and nonsmoker groups, with patients undergoing smoking cessation showing higher levels of

Table 1. Motoric Subtypes and Related Variables in Patients with Delirium.

			Analysis		
	Hyperactive ($n = 143$)	Hypoactive ($n = 67$)	χ^2/t^a	*df*	*P* Value
Age, y	70.99 ± 13.08	71.67 ± 13.33	−0.35	208	0.725
Sex, male/female, *n*	93/50	39/28	0.91	1	0.340
Comorbidities, *n* (%)					
Dementia	16 (11.2)	7 (10.4)	0.03	1	0.873
Hypnotic use	39 (27.3)	17 (25.4)	0.08	1	0.772
Opiate use	68 (47.6)	31 (46.3)	0.03	1	0.862
Neuroleptic use	52 (36.4)	16 (23.9)	3.25	1	0.072
Medical diagnosis, *n* (%)			2.25	7	0.945
Septic shock	8 (5.6)	4 (6.0)			
Cardiac disease	16 (11.2)	6 (9.0)			
Respiratory disease	4 (2.8)	1 (1.5)			
Malignancy	40 (28)	18 (26.9)			
Neurological disease	15 (10.5)	9 (13.4)			
Metabolic disease	6 (4.2)	1 (1.5)			
Infection	19 (13.3)	11 (16.4)			
Trauma or other	35 (24.5)	17 (25.4)			
Severity of delirium (total DRS-R98 scores)	22.58 ± 5.99	20.09 ± 5.54	2.82	208	0.005
Other domains of delirium					
DRS 1 (sleep)	2.07 ± 0.55	1.69 ± 0.67	3.44	208	0.001
DRS 4 (mood lability)	1.08 ± 0.81	0.73 ± 0.78	2.48	208	0.014
Length of hospital stay	29.55 ± 26.02	27.94 ± 22.03	0.44	208	0.661
3-month mortality, *n* (%)	37 (25.9)	12 (17.9)	1.62	1	0.203

Note: Values are provided as mean ± SD unless otherwise indicated. DRS, Delirium Rating Scale; DRS-R98, Delirium Rating Scale Revised–98.
[a]Unpaired *t* test was used for continuous variables, and χ^2 test or Fisher exact test was used for categorical variables.

sleep disturbances, mood lability, and agitation. The severity of delirium and the 3-month mortality and length of hospital stay did not significantly differ between the smoker and nonsmoker groups. Further analysis adjusted for confounding factors revealed that smoking was an independent predictor of hyperactive delirium (OR, 10.33; 95% CI, 2.31 to 46.09; $P = 0.002$; Table 3).

Figure 2 depicts the correlation between the severity of agitation (scores of RASS) and the amount of smoking (pack-years). A Spearman's correlation analysis revealed that the amount of smoking (pack-years) was positively correlated with the severity of agitation on the RASS ($r = 0.421$, $P = 0.003$) but not with the total scores on the DRS-R98 ($r = –0.014$, $P = 0.104$).

Discussion

The present study was the first to specifically focus on the impact of sudden nicotine withdrawal on the motoric subtypes of delirium in non-ICU hospitalized patients. The findings showed that hyperactive delirium was more prevalent than hypoactive delirium in patients referred for an abrupt change in mental status. Furthermore, patients with hyperactive delirium had higher levels of symptom severity and a higher 3-month mortality rate compared with patients with hypoactive delirium. In addition, nicotine withdrawal was associated with the hyperactive-type delirium and agitation.

Smoking and smoking cessation represent potentially modifiable risk factors of delirium in hospitalized patients. However, the present study did not find a significant association between nicotine withdrawal and the development of delirium above a clinical threshold, which is in agreement with the findings of a previous study.[24] On the other hand, after adjusting for potential confounders, the present study showed a strong association between nicotine withdrawal and the development of hyperactive delirium. A comparison of the smoker and nonsmoker groups in the present study revealed that smokers showed more severe agitation and greater degrees of sleep disturbance and mood lability, which are characteristic of hyperactive delirium. Delirium due to drug withdrawal is more likely to be of the hyperactive subtype, whereas metabolic encephalopathy is more likely to be related with the hypoactive subtype.[25] In addition, it has been suggested that different delirium subtypes may be associated with specific disruptions of activity within different neurotransmitter systems.[26] For example, anticholinergic intoxication states and delirium that result from traumatic brain injury are more often associated with the hyperactive than the hypoactive subtype. It has been proposed that changes in dopamine functioning can explain the different features of delirium. Excessive levels of dopamine may underlie the manifestations of hyperactive delirium, whereas deficiencies in dopamine activity may contribute to hypoactive delirium.[14,27] During nicotine withdrawal, there is decreased dopamine activity in the nucleus

Table 2. Demographic and Clinical Characteristics of Smokers and Nonsmokers.

			Analysis		
	Smokers ($n = 55$)	Nonsmokers ($n = 238$)	χ^2/t^a	*df*	*P* Value
Age, y	63.20 ± 16.29	72.36 ± 12.12	3.92	291	<0.001
Sex, male/female, No.	50/5	134/104	22.91	1	<0.001
Educational level, *n* (%)			5.05	3	0.168
Elementary school	13 (23.6)	68 (29.1)			
Middle school	6 (10.9)	46 (19.7)			
High school	16 (29.1)	56 (23.8)			
≥ University	20 (36.4)	64 (27.4)			
Comorbidities, *n* (%)					
Dementia	2 (3.6)	28 (11.8)	3.21	1	0.085
Hypnotic use	16 (29.1)	62 (26.1)	0.21	1	0.735
Opiate use	22 (40.0)	113 (47.5)	1.01	1	0.369
Neuroleptic use	16 (29.1)	75 (31.5)	0.12	1	0.872
Duration of smoking (pack-years)	38.98 ± 5.55	NA	NA		NA
Medical diagnosis, *n* (%)			10.85	7	0.145
Septic shock	2 (3.6)	10 (4.2)			
Cardiac disease	5 (9.0)	19 (8.0)			
Respiratory disease	1 (1.8)	5 (2.1)			
Malignancy	12 (21.8)	64 (26.9)			
Neurological disease	10 (18.2)	23 (9.7)			
Metabolic disease	1 (1.8)	9 (3.8)			
Infection	2 (3.6)	33 (13.9)			
Trauma or other	22 (40.0)	75 (31.5)			
Delirium, *n* (%)	39 (70.9)	171 (71.8)	0.019	1	0.870
Motoric types, hyperactive/hypoactive, *n*	37/2	106/65	15.70	1	0.001
Severity of delirium (total DRS-R98 scores)	20.20 ± 7.36	18.28 ± 6.13	−1.82	291	0.069
Severity of agitation					
RASS (–5 to 4)	0.73 ± 1.65	0.07 ± 1.24	–3.59	291	0.002
DRS 7 (0 to 3)	1.40 ± 0.98	0.95 ± 0.95	–3.19	291	0.002
Other domain of delirium					
DRS 1 (sleep)	1.98 ± 0.78	1.65 ± 0.95	−1.94	291	0.045
DRS 4 (mood lability)	1.02 ± 0.94	0.75 ± 0.76	–2.09	291	0.037
Length of hospital stay	33.02 ± 30.57	28.05 ± 25.91	−1.23	291	0.216
3-month mortality, *n* (%)	11 (20.0)	47 (19.7)	0.002	1	0.966

Note: Values are provided as mean ± SD unless otherwise indicated. DRS, Delirium Rating Scale; DRS-R98, Delirium Rating Scale Revised–98; NA, not applicable; RASS, Richmond Agitation Sedation Scale.
[a]Unpaired *t* test was used for continuous variables, and χ^2 test or Fisher exact test was used for categorical variables.

accumbens but increased dopamine release in the prefrontal cortex, which may be significant in the mediation of anxiety and agitation. Considering the role of the prefrontal cortex in the manifestation of delirium, this relationship may explain the higher incidence of hyperactive delirium in patients undergoing nicotine withdrawal.[28] It has also been shown that alterations in opiate neurotransmission contribute to withdrawal symptoms during smoking cessation. Animal studies have demonstrated that the somatic symptoms of nicotine withdrawal resemble those during opioid withdrawal, and similarly, human studies have reported that opioid antagonists can induce the development of nicotine withdrawal symptoms.[29,30] Thus, the sudden discontinuation of opioid use may influence the manifestation of delirium via the development of withdrawal symptoms that are similar to those experienced during the cessation of smoking.[31] Accordingly, a recent study reported several cases of opioid withdrawal–induced delirium.[32] The present findings suggest that nicotine withdrawal and hyperactive delirium share some common pathophysiologies that are mediated by changes in various neurotransmitter systems, including the dopamine, opioid, and cholinergic systems.

The present findings also demonstrated that the incidence of the hyperactive subtype was relatively higher (68.1%) than that of the hypoactive subtype, whereas previous studies have found a higher prevalence of hypoactive delirium; this discrepancy may be explained by the fact that old age and greater use of sedatives in ICU patients are associated with hypoactive delirium.[23,33] It is also possible that the true incidence of hypoactive delirium is higher than what was observed in the present study because the patients investigated in this study were referred for a behavioural change, which is relatively easy for physicians to notice. It has been shown that the symptoms of delirium are often neglected,[34] especially in patients who are not agitated.

Table 3. Logistic Regression Analysis of the Variables Associated with the Hyperactive Delirium Subtype in Patients with Confusion.

Factors	OR (95% CI)	*P* Value
Age (years)	1.00 (0.97 to 1.03)	0.994
Sex (male)	1.30 (0.65 to 2.61)	0.464
Educational level		
Elementary school	1.00	
Middle school	1.71 (0.63 to 4.69)	0.295
High school	0.66 (0.26 to 1.70)	0.393
$\geq$ University	1.32 (0.49 to 3.56)	0.578
Comorbidity		
Dementia	0.76 (0.28 to 2.07)	0.597
Hypnotics use	0.92 (0.46 to 1.85)	0.823
Opiates use	0.94 (0.51 to 1.75)	0.852
Medical diagnosis		
Septic shock	1.00 (0.25 to 4.07)	0.997
Cardiac disease	1.49 (0.47 to 4.73)	0.505
Respiratory disease	2.04 (0.19 to 21.59)	0.553
Malignancy	1.13 (0.48 to 2.67)	0.779
Neurological disease	0.75 (0.26 to 2.21)	0.600
Metabolic disease	4.21 (0.46 to 38.87)	0.204
Infection	0.96 (0.35 to 2.67)	0.944
Trauma or other	1.00	
Smoking cessation	10.33 (2.31 to 46.09)	0.002

Note: This model is adjusted for age, sex, education level, comorbidities and medical diagnosis. CI, confidence interval; OR, odds ratio.

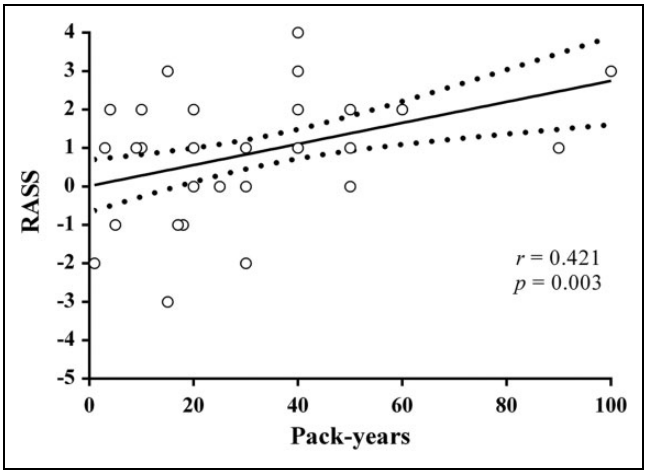

Figure 2. Correlation of scores on the Richmond Agitation Sedation Scale with the amount of smoking in the smoker group. Curved dotted lines indicate 95% confidence intervals. r = Spearman's correlation coefficient. RASS, Richmond Agitation Sedation Scale.

In the present study, the overall DRS-R98 scores were significantly higher in patients with the hyperactive than in those with the hypoactive subtype, which indicates that the symptoms associated with hyperactive delirium are more severe; this is consistent with previous findings.[35] Moreover, hyperactive delirium was associated with a poorer outcome in terms of mortality at 3 months compared with hypoactive delirium, as was also reported by a previous study.[36] That study suggested that oversedation of hyperactive patients may lead to other complications and to an acceleration of adverse events, which could, in turn, lead to high mortality. However, details regarding the hospital course were not sufficiently reported to accurately assess this possibility. Although other studies have found that the mixed type of delirium has the poorest prognosis,[28] the present study was not able to differentiate between the mixed and the hyperactive subtypes in this regard due to methodological limitations. Only a single assessment for the diagnosis and subtyping of delirium was performed, and as a result, the diagnostic stability of the pure hyperactive and mixed subtypes could not be confirmed. Furthermore, the stability associated with the subtyping of hyperactive and mixed delirium has been shown to be relatively lower than that of hypoactive delirium during episodes.[37] Thus, patients with the hyperactive and those with mixed delirium subtypes were combined into a single group in the present study.

Saravay et al.[38] found that behavioural problems such as the removal of catheter lines and falls, which are common in patients with hyperactive delirium, are associated with poor outcomes due to the use of physical restraints and the resultant interference with necessary treatments. However, data supporting the efficacy of pharmacological treatments for delirium remain elusive.[39] Multicomponent interventions failed to significantly lessen the duration and severity of delirium,[40] and absence of a single definitive treatment for delirium highlights the importance of its prediction and prevention. Delirium is not caused by a single factor but is the ultimate consequence of multiple factors.[41] Inouye and Charpentier[42] proposed a risk model with predisposing and precipitating factors, but most of these factors are patient dependent, limited, or not modifiable.[43] Thus, the identification and management of modifiable risk factors represent a possible strategy for the prevention of delirium.

The present findings provided convincing evidence that nicotine withdrawal and hyperactive delirium share common pathophysiologies and suggest that the concurrent management of these symptoms may be promising. Although it has been shown that nicotine replacement therapy (NRT) should not be routinely prescribed to inpatients due to cardiac side effects,[44] further randomized trial investigations examining appropriate strategies for the prevention and treatment of hyperactive delirium in patients with a history of heavy smoking are warranted. NRT and drugs such as clonidine and dexmedetomidine may be useful alternative pharmacological treatment options relative to the use of antipsychotics or physical restraint.[45-48] In addition, the early recognition and management of sleep-wake disturbances and mood lability in patients undergoing nicotine abstinence may also contribute to the prevention of hyperactive delirium.

In the present study, 83 patients could not be confirmed as having full syndromal delirium, although they displayed one or more symptoms of delirium. This state has been described as subsyndromal delirium (SSD), but it has yet to be well defined.[49] The mean DRS-R98 score of this group was 12.45, which indicates that these patients had at least one symptom of delirium but that its expression was milder than

that in patients with confirmed delirium. It has yet to be established whether SSD is a transitional state during the prodromal or resolving phase of delirium or an independent clinical syndrome that can be differentiated from delirium. However, previous studies have consistently reported that patients with SSD also have poorer outcomes, including longer hospital stays and higher mortality, than healthy controls.[50,51] Thus, SSD is also an important clinical focus and a target of prevention and management efforts.

The present study has several potential limitations that should be considered. First, no assessment of nicotine withdrawal-related symptoms was performed, so the differentiation of delirium and nicotine withdrawal symptoms may be unclear. Second, because these patients were referred to the CL psychiatry, the results of this study may not be generalized. In addition, a retrospective chart review performed by an unblinded, single reviewer might increase the risk of measurement bias. Third, follow-up assessments could not be performed, and thus changes in symptoms after the initial assessment may have been missed. Further prospective studies using multiple evaluations over regular intervals will provide clarity regarding this issue. Fourth, although there was no prescribed nicotine replacement therapy in patients according to the medical charts, the self-administration of nicotine gum or patches was not controlled for. Finally, the present study included relatively few events of smoking cessation and thus had a wide CI for the OR of smoking cessation to hyperactive delirium. A lack of the correction for multiple tests is another limitation. Further confirmatory studies that use larger samples are needed to confirm the present findings.

Conclusion

This study is the first to report an association between nicotine withdrawal and the hyperactive subtype of delirium in non-ICU hospitalized patients. Furthermore, hyperactive delirium was related to increased mortality in the present population. These findings suggest that clinicians should be aware of a patient's smoking history and the possibility of an acute reaction to smoking abstinence, and they should improve strategies for earlier nicotine withdrawal and the improved prediction of hyperactive delirium. In particular, the use of NRT should be considered as a preventative measure for hyperactive delirium in patients with a history of heavy smoking. However, nicotine withdrawal did not directly increase the risk of delirium or 3-month mortality in the present study. Supplementary evidence from future studies with a larger sample, various subtypes of delirium, and a more comprehensive approach to the analysis of the factors related to clinical outcomes may further characterize the manner in which smoking abstinence is related to delirium and mortality.

Declaration of Conflicting Interests

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